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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

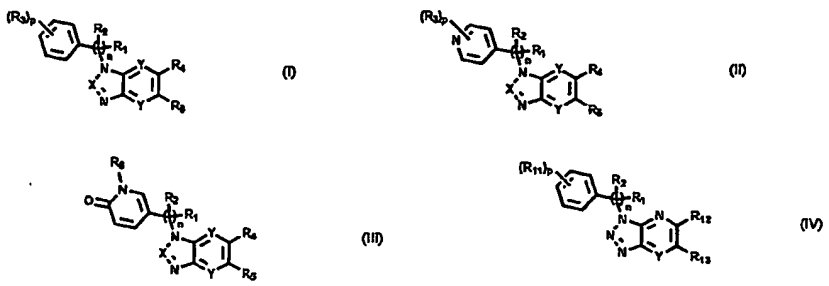
Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ARYLMETHYL TRIAZOLO AND IMIDAZOPYRAZINES AS C-MET INHIBITORS



(57) Abstract: The present invention relates to compounds of the Formulae (I) - (IV), wherein R1 - R6, R11 - R13, X and Y are defined herein, and their pharmaceutically acceptable salts. These compounds modulate the activity of c-Met and are therefore expected to be useful in the prevention and treatment of c-Met related disorders such as cancer.

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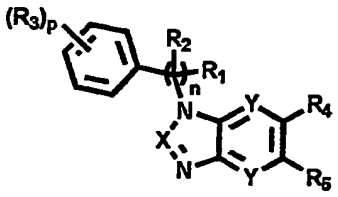
ABSTRACT

The present invention relates to compounds of the Formulae (I) – (IV), wherein R_1 – R_6, R_{11} – R_{13}, X and Y are defined herein, and their pharmaceutically acceptable salts. These compounds modulate the activity of c-Met and are therefore expected to be useful in the prevention and treatment of c-Met related disorders such as cancer.



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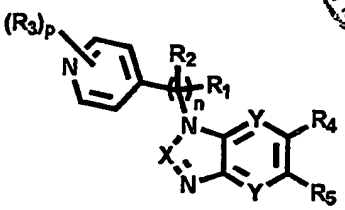

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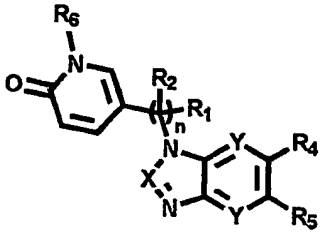
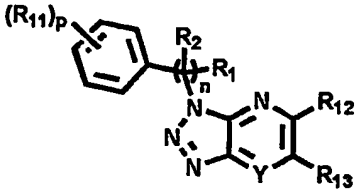


(III)



(IV)

ARYLMETHYL TRIAZOLO AND IMIDAZOPYRAZINES AS c-MET INHIBITORS

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 60/484,220, filed July 2, 2003, the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The following is offered as background information only and is not admitted to be prior art to the present invention.

[0003] Protein kinases ("PKs") are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell growth, differentiation and proliferation, *i.e.*, virtually all aspects of cell life in one way or another depend on PK activity. Furthermore, abnormal PK activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

[0004] The PKs can be conveniently broken down into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs).

[0005] One of the prime aspects of PTK activity is their involvement with growth factor receptors. Growth factor receptors are cell-surface proteins. When bound by a growth factor ligand, growth factor receptors are converted to an active form which interacts with proteins on the inner surface of a cell membrane. This leads to phosphorylation on tyrosine residues of the receptor and other proteins and to the formation inside the cell of complexes with a variety of cytoplasmic signaling molecules that, in turn, effect numerous cellular responses such as cell division (proliferation), cell differentiation, cell growth, expression of metabolic effects to the extracellular microenvironment, *etc.* For a more complete discussion, see Schlessinger and Ullrich, *Neuron* 9:303-391 (1992), which is incorporated by reference, including any drawings, as if fully set forth herein.

[0006] Growth factor receptors with PTK activity are known as receptor tyrosine kinases ("RTKs"). They comprise a large family of transmembrane receptors with diverse biological activity. At present, at least nineteen (19) distinct subfamilies of RTKs have been identified. An example of these is the subfamily designated the "HER" RTKs, which include EGFR (epithelial growth factor receptor), HER2, HER3 and HER4. These RTKs consist of an extracellular glycosylated ligand binding domain, a transmembrane domain and an intracellular cytoplasmic catalytic domain that can phosphorylate tyrosine residues on proteins.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/20062

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A01N 43/58, 43/60, 43/42, 43/40, 43/64, 43/52; A61K 31/495, 31/50, 31/44, 31/41, 31/415
US CL : 514/249, 300, 303, 338, 359, 394; 544/350; 546/117, 118, 268.4, 273.4; 548/257, 304.4
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/249, 300, 303, 338, 359, 394; 544/350; 546/117, 118, 268.4, 273.4; 548/257, 304.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: Structure search in REGISTRY file, answers crossed in CAPLUS file.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 46-33957 (KAWANO et al) 10 May 1971 (10.05.1971), column 2, lines 1-10.	1, 10
X	US 4,804,658 (MANLEY et al) 14 February 1989 (14.02.1989), column 4, lines 34-55, Example 15.	1, 10
X	GRAY et al. Pyridylethylation of Skatole, Benzotriazole and Benzimidazole. Journal of Organic Chemistry. November 1960. Vol. 25, No. 11, pages 1939-1943, especially page 1940, compound IV.	2
X	LOVELETTE et al. Studies in Nonbridgehead Fused Nitrogen Heterocycles - Fused 1,2,3-Triazoles. Journal of Organic Chemistry. December 1972. Vol. 37, No. 25, pages 4124-4128, especially page 4125.	1, 5
X --- Y	KHANNA et al. Facile, Regioselective Syntheses of N-Alkylated 2,3-Diaminopyridines and Imidazo[4,5-b]pyridines. Journal of Organic Chemistry. February 1995, Vol. 60, No. 4, pages 960-965, especially 960 in "Introduction" and page 964, synthesis of 1-[(2-methoxyphenyl)methyl]-1H-imidazo[4,5-b]pyridine.	1, 4, 10 --- 7, 8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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